## REMARKS

Claims 1-63 were pending in the application. Claims 11-12, 14-15, and 49-50 have been cancelled, without prejudice, and claims 1, 7, 8, 13, 16, 48 and 60 have been amended. Claims 22-47, 51-57, 59, and 61-63 have been cancelled herein, without prejudice, as being drawn to a non-elected invention. Accordingly, after the amendments presented herein have been entered, claims 1-10, 13, 16-21, 48, 58, and 60 will remain pending. Support for the amendments to the claims can be found throughout the specification and in the claims as originally filed.

Support for the amendments to claims 1, 7, 8, 13, 16, 48, and 60 can be found throughout the specification and claims as originally filed. In particular, support for the amendments to claims 1, 8, and 13 may be found at page 1, lines 32-34; at page 14, lines 26-31; and at page 7, lines 34-36 of the specification. Support for the amendment to claim 13 may also be found at page 1, line 15 of the specification.

*No new matter has been added.* Any amendment and cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

### *Searches*

The Examiner objected that "neither one of the GenBank searches has been considered because they are not publications." Furthermore, the Office Action indicates that "GenBank Accession No. U80818 has not been considered because no copy of the reference is in this file or the parent file Serial No. 09/044, 273."

Applicant provides herewith, as Appendix A, a copy of Accession No. U80818.

### *Rejection of Claims 1-10, 13-21, 48-50, 58, and 60 Under 35 U.S.C. §112, Second Paragraph*

The Examiner has rejected claims 1-10, 13-21, 48-50, 58, and 60 under 35 U.S.C. §112, second paragraph as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

Applicant respectfully traverses the aforementioned rejection on the grounds that the instant claims particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Rejection of the Phrase "at least about 60% homologous to" (Claims 1, 8, and 13)

The Examiner is of the opinion that the phrase "at least about 60% homologous to" is vague and indefinite because the metes and bounds of the claims are not clear.

Applicant respectfully traverses the foregoing rejection. However, in the interest of expediting prosecution and in no way conceding to the Examiner's rejections, Applicant has amended claims 1 and 8 to remove the term "about" and more particularly recite "at least 90% homologous to," thereby rendering the foregoing rejection moot. Claim 13 no longer recites the rejected phrase. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Rejection of "HICP" (Claims 1, 7, 10, 20, 21, 48, 49, 50 and 58)

According to the Examiner, "the recitation of 'HICP' is vague and indefinite. The term does not describe a structure that can [be] used to determine whether a given molecule is embraced by the claims."

With respect to the term "HICP," Applicant respectfully traverses the rejection and submits that, based on the teachings in the specification and the knowledge generally available in the art, one of skill in the art would find this phrase to be clear and definite. To begin with, Applicant has amended claim 1 to recite "heparin-induced, CNN-like protein (HICP)." Applicant respectfully submits that case law has repeatedly held that the inventor's practitioner and the inventor may be their own lexicographers and grammarians. *See W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 1558, 220 U.S.P.Q. 303, 316 (Fed. Cir. 1983) (M.P.E.P. §2173.01). In the present case, Applicant has elected to be his own lexicographer, have coined the term "HICP" and have defined this term as follows,

> [t]he present invention provides a novel nucleic acid molecule which encodes a protein, referred to herein as Heparin-Induced, CCN-like protein (HICP), which is capable of modulating a variety of cellular processes including cell proliferation (see page 1, lines 32-34 of the specification).

Applicant submits that it is a fundamental principle of 35 U.S.C. §112, second paragraph that applicants may be their own lexicographers and may define in the claims what they regard as their invention, essentially in whatever terms they choose, so long as the terms are not used in ways that are contrary to accepted meanings in the art. In view of the definition in Applicant's specification, the skilled artisan would find the term "HICP" to be clear and definite. Accordingly, Applicant respectfully requests that the aforementioned rejection be reconsidered and withdrawn.

Rejection of Phrase "specifically detects" (Claim 7)

The Office Action indicates that the phrase " 'specifically detects' is vague, indefinite, and incomplete because specificity of detection depends upon the presence of other, unmentioned molecules within the reaction mixture." Applicant respectfully traverses the foregoing rejection. Applicant teaches that the invention features HICP nucleic acid molecules which specifically detect HICP nucleic acid molecules relative to nucleic acid molecules encoding non-HICP proteins. In this regard, Applicant also discloses numerous hybridization methods to specifically detect such HICP nucleic acid molecules (see, for example, page 1, lines 14-33 of the specification). However, in the interest of expediting prosecution and in no way conceding to the Examiner's rejections, Applicant has amended claim 7 to recite "is capable of specifically hybridizing to." As such, Applicant teaches at page 3 of the specification that the invention features a HICP nucleic acid molecule which hybridizes to a HICP nucleic acid molecule, for example, a nucleic acid molecule comprising nucleotides 1-883 of SEQ ID NO:1. In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Rejection of the "modulation" activities (Claim 13)

The Examiner indicates that the phrases "modulate cell proliferation," "modulate a growth factor signaling pathway," "modulate the activity of CTGF or PDGF" and "modulate a heparin-induced response in a heparin-responsive cell" are vague and indefinite because the instant application does not distinguish between modulation and non-modulation. Applicant

respectfully traverses on the grounds that claim 13 particularly points out and distinctly claims the subject matter which Applicant regards as the invention.

With respect to the phrases "modulate cell proliferation" and "modulate a heparin-induced response in a heparin-responsive cell," the specification teaches that the HICP molecules of the invention modulate cell proliferation, for example, by playing a role in growth inhibition in heparin responsive cells (see page 7, lines 8-20 of the specification). Applicant also teaches that HICP modulates (*e.g.*, mediates) the antiproliferative effect of heparin; and heparin has been shown to suppress proliferation of various cell types, *e.g.*, vascular smooth muscle cells (VSMC). Without being limited by theory, Applicant describes a proposed mechanism by which heparin inhibits proliferation of cells, *e.g.*, by binding to receptors on the cell surface which leads to selective modulation of signal transduction pathways and altered transcription of specific growth regulatory genes. HICP proteins are expressed at increased levels in heparin-treated cells, and play a role in the antiproliferative effect of heparin on heparin-responsive cells. Thus, the HICP molecules are capable of inhibiting proliferation of heparin-responsive cells, *e.g.*, VSMC. Moreover, the HICP protein, by acting as a growth factor antagonist, *e.g.*, a CTGF antagonist, can modulate (*e.g.*, inhibit) aberrant or abnormal cell proliferation, cell motility and/or extracellular matrix production. Therefore, in the interest of expediting prosecution and no in way conceding to the Examiner's rejections, Applicant has amended subsections (i) and (ii) of claim 13 to recite "inhibiting cell proliferation" and "acting as a growth factor antagonist," thereby rendering the foregoing rejection moot.

With regard to the phrase "modulate a growth factor signaling pathway," Applicant teaches that the HICP molecules of the invention are capable of modulating the activity of one or more proteins involved in a growth factor signaling pathway, *e.g.*, a CTGF signaling pathway (see page 7, lines 21-28 of the specification). Applicant teaches that the HICP molecules of the invention may modulate the activity of one or more proteins by interfering with or preventing signal transduction. For example, a HICP molecule can interfere with the activity or one or more proteins involved in a growth factor signaling pathway by acting as a growth factor antagonist, thereby inhibiting or suppressing a growth factor induced activity, *e.g.*, proliferation, cell motility or extracellular matrix production. Therefore, in the interest of expediting prosecution and no in way conceding to the Examiner's rejections, Applicant has amended

subsection (ii) of claim 13 to recite "acting as a growth factor antagonist," thereby rendering the foregoing rejection moot.

With respect to the phrase, "modulate the activity of connective tissue growth factor (CTGF) or platelet derived growth factor (PDGF)," Applicant teaches that studies have suggested that several growth factors may play a role, not only in the normal development, growth and repair of human tissue, but also may be involved pathologically in diseases or disorders characterized by uncontrolled tissue growth. For example, both PDGF and CTGF are known to be mitogens and chemotactic agents for connective tissue cells. In addition, both PDGF and CTGF have been implicated in disorders in which there is an overgrowth of connective tissue cells, such as cancer, fibrotic diseases and atheroclerosis. Applicant also teaches that because CTGF is known to be a mitogen, a chemotactic agent for connective tissue and a stimulator of extracellular matrix production, this growth factor has been implicated as a major factor involved diseases and disorders characterized by hyperproliferation of connective tissue cells (page 7, lines 28-32 of the specification). Thus, the HICP protein, by acting as a growth factor antagonist, *e.g.*, a CTGF antagonist, can modulate (*e.g.*, inhibit) aberrant or abnormal cell proliferation, cell motility and/or extracellular matrix production. Thus, HICP molecules (or modulators thereof) of the present invention can be used to treat various fibroproliferative disorders in which fibrosis is an important feature of the pathology, *e.g.*, abnormal scarring, keloidosis and kidney and lung fibrosis. Therefore, in the interest of expediting prosecution and no in way conceding to the Examiner's rejections, Applicant has amended subsections (iv) and (v) of claim 13 to recite "acting as a connective tissue growth factor (CTGF) agonist" and "acting as a platelet derived growth factor (PDGF) agonist," thereby rendering the foregoing rejection moot.

In view of the teachings in Applicant's specification, the skilled artisan would find the above phrases and terms to be clear and definite. Accordingly, Applicant respectfully requests that the aforementioned rejections be reconsidered and withdrawn.

Rejection of "CTGF" and "PDGF" (Claim 13)

The Office Action indicates that the recitation of "CTGF" and "PDGF" is vague and indefinite because the term is not defined. Applicant has amended claim 13, as suggested by the Examiner, to recite the full-terms for CTGF and PDGF.

Claim 48

The Examiner indicates that claim 48 is "vague and indefinite because it claims more than was elected. Only the methods for detecting nucleic acids were included in the elected Group (*i.e.* Group I)."

Applicant traverses the foregoing rejection, because Applicant believes that claim 48 should be grouped in Group I. In particular, claim 48, as amended herein, is directed to a method for detecting the presence of HICP activity in a biological sample comprising contacting a biological sample with an agent capable of detecting an indicator of HICP activity such that the presence of HICP activity is detected in the biological sample, wherein the agent is a labeled nucleic acid probe capable of hybridizing to HICP mRNA. Thus, Applicant has amended claim 48 to specify the agent used in the claimed method. In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Rejection of the Phrases in Claim 58

The Examiner indicates that the phrases "aberrant modification or mutation of a gene encoding HICP protein," "mis-regulation" of said gene, and "aberrant post-translational modification of a HICP protein" are "vague and indefinite because the metes and bounds of the claim are not clear within the context of the claim."

Applicant respectfully traverses the rejection and submits that, based on the teachings in the specification and the knowledge generally available in the art, one of skill in the art would find these phrases to be clear and definite. To begin with, as the phrase implies, "aberrant modification or mutation of a gene encoding a HICP protein" refers to a change in the gene encoding the HICP protein as compared to the wild-type gene. Applicant specifically teaches standard techniques for introducing such a mutation into a HICP molecule, such as site-directed mutagenesis and PCR-mediated mutagenesis (page 17, lines 27-33 of the specification). The instant specification also describes that conservative amino acid substitutions may be made at one or more predicted non-essential amino acid residues and defines such conservative amino acid substitutions. Applicant also teaches that mutations can be introduced randomly along all or part of a HICP coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for HICP biological activity to identify mutants that retain activity. Following

mutagenesis of a HICP molecule, the encoded protein can be expressed recombinantly and the activity of the protein can be determined. In addition, the instant specification teaches how such a mutant HICP proteins can be assayed for the ability to modulate cellular proliferation, either *in vitro or in vivo*.

Likewise, one of skill in the art would readily understand the term "mis-regulation of said gene" to mean a change in the expression of the gene, which could occur, for example, at the transcriptional or translational level. Furthermore, one of skill in the art would also understand the phrase "aberrant post-translational modification of a HICP protein" to mean modifications to the HICP protein, as compared to the wild-type, that occur following translation.

It is Applicant's position that these phrases are clearly described in the section of the specification describing multiple assays that can also be used to identify genetic alterations in a cell sample. For example, Applicant teaches methods for detecting in a sample of cells,

> the presence or absence of a genetic lesion characterized by at least one of an alteration affecting the integrity of a gene encoding a HICP protein, or the misexpression of the HICP gene. For example, such genetic lesions can be detected by ascertaining the existence of at least one of 1) a deletion of one or more nucleotides from a HICP gene; 2) an addition of one or more nucleotides to a HICP gene; 3) a substitution of one or more nucleotides of a HICP gene, 4) a chromosomal rearrangement of a HICP gene; 5) an alteration in the level of a messenger RNA transcript of a HICP gene, 6) ***aberrant modification of a HICP gene, such as of the methylation pattern of the genomic DNA***, 7) the presence of a non-wild type splicing pattern of a messenger RNA transcript of a HICP gene, 8) a non-wild type level of a HICP-protein, 9) allelic loss of a HICP gene, and 10) ***inappropriate post-translational modification of a HICP-protein***. As described herein, there are a large number of assay techniques known in the art which can be used for detecting lesions in a HICP gene (see page 49, line 23 through page 50, line 2 of the specification).

In view of the foregoing, Applicant respectfully traverses the rejection and submits that, based on the teachings in the specification and the knowledge generally available in the art, one of skill in the art would find these phrases to be clear and definite.

***Rejection of Claims 1-8, 13, and 16-20 Under 35 U.S.C. §112, First Paragraph***

The Examiner has further rejected claims 1-8, 13, and 16-20 under 35 U.S.C. §112, first paragraph because the specification, while being enabling for those sequences recited with specificity, "does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims." According to the Examiner,

> [o]ne of skill in the art would be obliged to perform undue experimentation to determine which variants might have activity and/or use because the instant application does not provide guidance to one of skill in the art as to which types of variants might have activity and/or use.

With respect to claims 1 and 8, directed to an isolated nucleic acid molecule which encodes a heparin-induced, CNN-like protein (HICP), comprising a nucleotide sequence at least 90% homologous to a nucleotide sequence of SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3, or a complement thereof, wherein said nucleic acid molecule encodes a protein having at least one of the following activities: i) inhibiting cell proliferation; ii) acting as a growth factor antagonist; iii) inhibiting growth in heparin responsive cells; iv) acting as a connective tissue growth factor (CTGF) agonist; or v) acting as a platelet derived growth factor (PDGF) agonist; and claims depending therefrom, Applicant traverses the foregoing rejections for the following reasons.

Although the foregoing rejection pertains to enablement, Applicant wishes to draw the Examiner's attention to Example 14 of the *Revised Interim Written Description Guidelines Training Materials,* which provides that "***[t]he procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art.***" In particular, according to the *Guidelines,* a claim directed to variants of a protein having SEQ ID NO:3 "that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B" with an accompanying specification that discloses a single species falling within the claimed genus, satisfies the requirements of 35 U.S.C. §112, first paragraph for written description. The rational behind the foregoing conclusion, as presented by the *Written Description Guidelines*, is that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and

because of the presence of an assay which Applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity."

Similarly, in the present case, claims 1, 8, and 13 are directed to a nucleic acid molecule comprising a nucleotide sequence which is at least 90% identical to a nucleotide sequence of SEQ ID NO:1, 2, or 3, or a complement thereof, wherein said nucleic acid molecule encodes a protein having at least one of the following activities: i) inhibiting cell proliferation; ii) acting as a growth factor antagonist; iii) inhibiting growth in heparin responsive cells; iv) acting as a connective tissue growth factor (CTGF) agonist; or v) acting as a platelet derived growth factor (PDGF) agonist. Applicant has disclosed in the instant specification assays for identifying all of the at least 90% identical variants of SEQ ID NO:1, 2, or 3. Moreover, Applicant has described assays that may be used to test whether these variants have one of the above-described HICP activities (see page 51, line 10 through page 54, line 37 of the specification). Moreover, as indicated by the Guidelines, "procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art."

Thus, based on the teachings in Applicant's specification and the knowledge generally available in the art at the time of the invention, the skilled artisan would be able to make and use the claimed invention using only routine experimentation. Applicant therefore respectfully request withdrawal of the foregoing rejection.

***Rejection of Claims 1-21, 48-50, 58 and 60 Under 35 U.S.C. §101***

The Examiner has rejected claims 1-21, 48-50, 58, and 60 under 35 U.S.C. § 101. According to the Examiner,

> [t]he instant application does not disclose a specific, substantial, and credible utility...The instant application does not disclose enough information to one of skill in the art given the instant application.

Applicant respectfully traverses the foregoing rejection. It is Applicant's position that a specific and substantial utility has clearly been set forth in the instant specification that would have been credible to one of skill in the art at the time of the invention. The instant specification teaches that the claimed nucleic acid molecules, and proteins encoded by these molecules, are capable of modulating a variety of cellular processes including cell proliferation. Applicant

further teaches that the claimed HICP molecules are part of a signal transduction pathway in which HICP functions as part of an antiproliferation mechanism, thus, HICP molecules of the present invention can be used to modulate proliferation of heparin-responsive cells (*e.g.*, VSMC) and thus to treat proliferative disorders such as cardiovascular disorders (page 2, lines 3-11 of the specification). Furthermore, the present application teaches that the HICP molecules of the present invention play a role in growth factor signaling pathways, *e.g.*, CTGF signal pathway, and are capable of interfering with growth factor signaling to thereby inhibit or suppress growth factor induced proliferation, cell motility and extracellular matrix production. Thus, HICP molecules can be used to modulate cell proliferation, cell motility and extracellular matrix production in various cell types and thus can be used to treat other disorders characterized by aberrant or abnormal cell proliferation and fibroproliferative disorders, *e.g.*, fibrotic disorders (page 2, lines 12-19 of the specification). In particular, the present invention teaches that the claimed nucleic acid molecules may be used to detect genetic lesions in the HICP gene, thereby determining if a subject with the lesioned gene is at risk for a disorder characterized by aberrant or abnormal HICP nucleic acid expression or HICP protein activity. The present invention further teaches that the claimed nucleic acid molecules may be used in screening assays to identify modulators of the HICP molecules that may be used in, for example, treating a subject suffering from a disorder characterized by aberrant or abnormal cell proliferation and fibroproliferative disorders.

The skilled artisan would find the foregoing *specific and substantial utilities* asserted in Applicant's specification to be *credible* based on the evidence set forth in the specification. In view of the foregoing, it is evident that Applicant's invention has a well-established utility that would have been readily apparent to one of skill in the art at the time of the invention. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection under 35 U.S.C. §101.

***Rejection of Claims 1-21, 48-50, 58 and 60 Under 35 U.S.C. §112, First Paragraph***

The Examiner has rejected claims 1-21, 48-50, 58 and 60 under 35 U.S.C. §112, first paragraph "as failing to comply with the enablement requirement."

Applicant respectfully traverses the foregoing rejection on the basis that Applicant's specification discloses sufficient guidance as to how one of skill in the art would use the claimed invention. As indicated above, Applicant has identified that the molecules of the present invention are useful in diagnosing, prognosing, or treating disorders characterized by aberrant or abnormal cell proliferation and fibroproliferative disorders, *e.g.*, fibrotic disorders (see page 2, lines 12-19 of the specification). Moreover, Applicant's specification discloses ample guidance as to how one of skill in the art would use the claimed invention and the compounds identified using the claimed invention (see, for example, the screening assays (page 42, line 31 through page 48, line 16), the diagnostic assays (page 48, line 19 through page 51, line 7), and the methods of treatment (page 51, line 10 through page 54, line 37) taught by Applicant in the instant specification). Thus, one of ordinary skill in the art reading the foregoing teachings in Applicant's specification would have been able to make and use the claimed invention using only routine experimentation.

In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the foregoing 35 U.S.C. §112, first paragraph rejection.

***Rejection of Claims 7, 10, and 12 Under 35 U.S.C. §102(b)***

The Examiner has rejected claims 7, 10 and 12 under 35 U.S.C. §102(b) as being clearly anticipated by Bonaldo *et al.* (Genome Res. 6:791 (1996)). According to the Office Action, "Bonaldo *et al.* discloses a DNA that is 99.4% identical to SEQ ID NO:1, positions 1534-1708...Thus, the DNA of Bonaldo *et al.* is embraced by the claims."

Applicant respectfully traverses the rejection and submits that unlike SEQ ID NO:1, which is a nucleic acid sequence that encodes a ***functional HICP protein***, the Bonaldo *et al.* reference teaches large-scale sequencing of cDNA libraries without teaching or suggesting key structural features of the clones, such as whether the disclosed clones contain a coding sequence. In particular, claims 7 and 10, which depend from claim 1, are directed to isolated nucleic acid molecules which encode a HICP protein. However, ***Bonaldo et al. does not teach a sequence that encodes a HICP protein.*** Moreover, the sequence disclosed in the Bonaldo *et al.* reference, Accession No. BQ195526, does not have significant overall homology with the instantly claimed nucleotide sequences. Specifically, the sequence shown in BQ195526 is merely 32.3%

identical to SEQ ID NO: 1, based on a global alignment. Thus, contrary to the Examiner's assertion, the Bonaldo *et al.* reference fails to anticipate the subject matter of the pending claims.

Applicant has cancelled claim 12, without prejudice, thereby obviating the rejection with respect to claim 12. In view of the foregoing, Applicant respectfully requests withdrawal of the rejection.

## SUMMARY

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. MBI-004CN from which the undersigned is authorized to draw.

Dated: March 22, 2004

Respectfully submitted,

By _____

Hathaway Pease
Registration No.: 46,488
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicant